1 539 277

PATENT SPECIFICATION (11) 1 539 277

(21) Application No. 39402/76 (22) Filed 22 Sept. 1976
(23) Complete Specification filed 16 Sept. 1977
(44) Complete Specification published 31 Jan. 1979
(51) INT CL² C07D 223/04 A61K 31/55
(52) Index at acceptance
C2C 1731 215 220 22Y 246 250 251 25Y 29X 29Y 30Y 365 36Y 623 662 802 80Y WH

(72) Inventors JOHN FREDERICK CAVALLA and RICHARD ARTHUR FRANKLIN

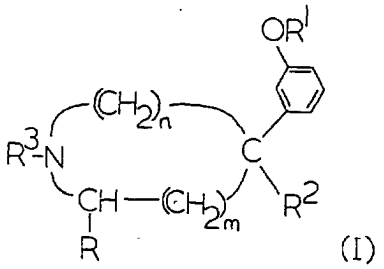
(19)

(54) HEXAHYDRO-1H-AZEPINES

(71) We, JOHN WYETH & BROTHER LIMITED, a British Company of Huntercombe Lane South, Taplow, Maidenhead, Berkshire, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to hexahydro - 1*H* - azepines, to processes for their preparation and to pharmaceutical compositions containing them.

U.K. Specification No. 1,285,025 discloses hexahydroazepine derivatives of the general formula



(I)

and acid addition and quaternary ammonium salts thereof, in which R^1 is a hydrogen atom, a lower alkyl radical, a benzyl radical or a lower alkanoyl radical, R^2 is a lower alkyl radical, R^3 is a hydrogen atom, a lower alkyl, lower alkenyl, lower alkynyl, cyclopropylmethyl, lower alkanoyl, lower alkoxycarbonyl, formyl, phenacyl or phenethyl group both of which may be substituted in the benzene ring or a β - benzoylethyl radical which may be substituted in the benzene ring, n is the integer 3 or 4, m is 0 or the integer 1 with the proviso that n+m is always equal to 4, R is a hydrogen atom or lower alkyl radical when m is 0 or a hydrogen atom only when m is the integer 1.

Acid addition salts of the hexahydroazepines specifically mentioned are those formed from pharmaceutically acceptable acids, e.g. hydrochloric, sulphuric and maleic acids. The prior specification mentions that the hexahydroazepines exhibit pharmaceutical activity, e.g. analgesic activity. A particular compound mentioned is *m* - (3 - ethylhexahydro - 1 - methyl - 1*H* - azepin - 3 - yl)phenol.

We have now found that the acid addition salt of *m* - (3 - ethylhexahydro - 1 - methyl - 1*H* - azepin - 3 - yl)phenol with embonic acid is of particular advantage as an analgesic agent since it has prolonged activity when administered, for example, intramuscularly. Testing in experimental animals has shown that the embonate produces analgesia of a longer duration than the more common acid addition salts such as the hydrochloride.

Accordingly, the present invention provides an acid addition salt of *m* - (3 - ethylhexahydro - 1 - methyl - 1*H* - azepin - 3 - yl)-phenol with embonic acid [i.e. an embonate of *m* - (3 - ethylhexahydro - 1 - methyl - 1*H* - azepin - 3 - yl)phenol]. Embonic acid, otherwise known as pamoic acid, is a dibasic acid and hence it is possible to form both mono- or di - salts with *m* - (3 - ethylhexahydro - 1 - methyl - 1*H* - azepin - 3 - yl)phenol. Both salts are included within the invention *m* - (3 - ethylhexahydro - 1 - methyl - 1*H* - azepin - 3 - yl)phenol contains an asymmetrical carbon atom and hence it can exist in optically active forms or as a mixture of such forms, e.g. the racemate. Salts with both optically active forms and with mixtures of such forms, especially the racemate, are included in this invention. The racemate is herein also termed "meptazinol". The acid addition salts of the present invention may be prepared in known manner, e.g. by treating the free base with embonic acid. If the free base is in the form of an optical isomer the acid addition salt will also be in the form of an optical isomer while if the free base is in the form of the racemate the acid addition salt will also be a racemate.

The present invention also provides a pharmaceutical composition having analgesic activity comprising an embonate of *m* - (3 - ethylhexahydro - 1 - methyl - 1*H* - azepin - 3 - yl)phenol in association with a pharmaceutical carrier.

Although the composition may be in any conventional form such as tablets and capsules for oral administration and suspensions

for oral and parenteral administration it is preferable that the composition is in the form of a suspension for intramuscular administration. Such compositions have the advantage of prolonged activity. The carrier for suspensions suitable for intramuscular administration may be, for example any of those described in the literature (see, for example, pages 517 to 537 of The Theory and Practice of Industrial Pharmacy, edited by Lachman, Lieberman and Kanig, published, 1970 by Lea and Febiger). For example, the suspension may be a sterile aqueous suspension containing, for example, suspending agents (hydrocolloids) to increase the viscosity. Examples of suitable suspending agents include gelatin, acacia, polyvinylpyrrolidone and cellulose derivatives such as methyl cellullose, sodium carboxymethyl - cellulose and hydroxypropylmethyl cellulose. The suspensions may contain other formulation adjuncts such as surface active agents (e.g. polyoxyethylene sorbitan mono - oleate, lecithin and polyoxyethylene/polyoxypropylene copolymers), flocculating agents (e.g. monosodium citrate and aluminium trichloride), antibacterials (e.g. methyl and propyl hydroxybenzoates and benzyl alcohol) and substances added to alter the tonicity of the suspension (e.g. sodium chloride and dextrose).

Preferably the pharmaceutical composition is in unit dosage form. In such form the composition is sub-divided in unit doses containing appropriate quantities of the active ingredient; the unit dosage form can be a packaged composition, the package containing specific quantities of compositions, for example packeted vials or ampoules. The quantity of active ingredient in a unit dose of composition may be varied or adjusted from about 5 mg to about 500 mg according to the particular need and the activity of the active ingredient.

In a standard pharmacological test for analgesic activity (B. Weiss et al, J. Pharm and Expt. Therap. 1964, *143*, 169) meptazinol hydrochloride was compared with the embonate in a two monkey crossover study. Both drugs were administered intramuscularly. The hydrochloride was administered at 5 mg/kg and the ambonate was administered at 3.7 mg/kg (calculated as base for each compound). After administration of the hydrochloride analgesia was seen starting at 8 to 12 minutes and lasting for 2.2 to 2.9 hours. The onset of analgesia after embonate administration varied from 24 to 28 mins. and lasted for 3.5 to 3.8 hours. This date indicated a longer duration of analgesic effect for the embonate salt.

The prolonged activity of the compositions of the present invention have also been demonstrated in another procedure. In this procedure tritium labelled meptazinol and the embonate of meptazinol were administered intramuscularly to monkeys in the form of suspensions in sodium carboxymethyl cellulose. In addition ^3H labelled meptazinol hydrochloride was administered intramuscularly to monkeys in the form of a solution in isotonic saline. Blood samples were collected in heparinized containers at varying times after administration of the radioactive drugs. The radioactivity due to unconjugated meptazinol in each plasma sample was then determined by liquid scintillation counting following extraction into toluene. It was found that the rate of decrease in radioactivity (equivalent to the rate of drug elimination from the plasma) was slowest with the suspension of the embonate and fastest with the solution of the hydrochloride. The terminal half lives for the three drugs are:

embonate suspension: 3.10 hours
suspension of the base: 1.75 hours
solution of the hydrochloride: 0.95 hours.

The following Examples illustrate the invention.

Example 1

Meptazinol embonate

Meptazinol hydrochloride (2.7 g 0.01 mole) in water (25 ml) was added to a stirred cooled solution of embonic acid (1.94 g 0.005 mole) in 0.05 *M* sodium carbonate (100 ml). The solid that precipitated was filtered off, resuspended in water (100 ml) and stirred for several hours. After filtering the solid was dried at 30°C and 0.1 mm for 24 hrs. to give the title compound.

Analaysis:
Found:
C, 73.0; H, 7.26; N, 3.16.
$(C_{15}H_{23}NO)_2\ C_{23}H_{16}O_6\ .\ H_2O$ requires:
C, 72.9; H, 7.4; N, 3.2%

The ratio of meptazinol to embonic acid of 2:1 was confirmed by n.m.r. and quantitative glc.

Example 2

Suspension for intramuscular administration

A sterile suspension was prepared of the following ingredients:—

	w/w%
Embonate of meptazinol	5.00
High viscosity sodium carboxymethyl cellulose	0.30
Tween 80 (polyethylene oxide sorbitan mono - oleate; 'Tween' is a Registered Trade Mark)	1.50
Methyl hydroxybenzoate	0.06
Propyl hydroxybenzoate	0.03
Distilled water to	100.00

WHAT WE CLAIM IS:—

1. An acid addition salt of *m* - (3 - ethylhexahydro - 1 - methyl - 1*H* - azepin - 3 - *yl*)phenol with embonic acid.
2. Meptazinol embonate.

3. A process for preparing a compound claimed in claim 1 which comprises reacting *m* - (3 - ethylhexahydro - 1 - methyl - 1*H* - azepin - 3 - yl)phenol with embonic acid.

4. A process for preparing a compound as claimed in claim 1 substantially as hereinbefore described with reference to Example 1.

5. A compound whenever prepared by the process of Claim 3 or 4.

6. A pharmaceutical composition comprising a compound claimed in any one of claims 1, 2 and 5 in association with a pharmacetical carrier.

7. A pharmaceutical composition as claimed in claim 6 in the form of a suspension for intramuscular administration.

8. A pharmaceutical composition as claimed in claim 6 or 7 in unit dosage form.

9. A pharmaceutical composition substantially as hereinbefore described with reference to Example 2.

K. J. S. BROWN,
Chartered Patent Agent.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1979
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.